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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

IN RE: CHANTIX (VARENICLINE) PRODUCTS LIABILITY LITIGATION	Master File No. 2:09-CV-2039-IPJ MDL No. 2092
This Document Relates To: ALL CASES	

DEFENDANT PFIZER INC'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION TO EXCLUDE OPINIONS OFFERED BY PLAINTIFFS' EXPERT DR. SHIRA KRAMER

(MEMORANDUM 3 OF 6)

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PRELIMINARY STATEMENT

Plaintiffs' expert Dr. Shira Kramer offers a general causation opinion regarding Chantix and serious neuropsychiatric adverse events based on a so-called "weight of evidence" approach. Dr. Kramer's methodology amounts to a subjective and unscientific interpretation of select data that renders her opinions unreliable and invalid.

Dr. Kramer's general causation opinion relies extensively on uncontrolled data, including post-marketing adverse event reports, which cannot establish a statistical association between Chantix and neuropsychiatric events. Because neuropsychiatric adverse events occur regularly in the general population, and at increased rates among smokers trying to quit, a control group is needed to determine whether the rates of such events in persons taking Chantix are different from the rates in smokers trying to quit without Chantix.

To the extent she cites controlled clinical trial and/or observational data, Dr. Kramer's approach is to abandon the principal of statistical significance, cherry pick those studies showing a numerical increase in the Chantix group, and interpret those studies as establishing an increased risk. She ignores studies that go in the other direction, where differences in serious neuropsychiatric adverse events favor Chantix. She also disregards other considerations relevant to a finding of causation, such as the presence or absence of a dose-response relationship.

Dr. Kramer's selective methodology cannot establish a reliable association between Chantix and serious neuropsychiatric events within the error rate that is generally accepted in the medical community, and it is not a reliable basis on which to conclude that any association reflects a causal relationship.

Beyond general causation, Dr. Kramer intends to offer opinions on additional subjects for which she is unqualified. Dr. Kramer offers opinions about what Pfizer "knew" and when with respect to the neuropsychiatric safety of Chantix, which are not the proper subject of expert testimony. And she claims that she may offer opinions about the adequacy of the Chantix labels, an area in which she has no relevant background or experience. As a result, the Court should exclude her causation opinion in its entirety and limit her testimony in other areas.

STATEMENT OF FACTS

I. QUALIFICATIONS, KNOWLEDGE AND EXPERIENCE

Dr. Kramer is the President of Epidemiology International, Inc., an epidemiological research and consulting firm. *See* Expert Report of Shira Kramer, PhD, MHS, at 6 ("Kramer Rep.") (Ex. 11). She is not a medical doctor, so she never has treated patients or prescribed medications. *See* Deposition of Dr. Shira Kramer, Mar. 9, 2012, at 127 ("Kramer Dep.") (Ex. 41). She never has published papers in the peer-reviewed medical literature on smoking cessation, the

psychiatric effects of quitting smoking, or psychiatric effects of medications. *See id.* at 68-70.

Dr. Kramer's causation opinion rests on her analysis of issues in which she has virtually no education or experience. For example, she never has been the principal investigator responsible for the design or analysis of a clinical trial, and she has no clinical trial experience at all in the last 25 years. *See id.* at 127-28, 131. Dr. Kramer also has limited expertise in statistics. She does not have a degree in statistics and never has taught on the subject. *See id.* at 104-05. She can conduct only rudimentary calculations such as relative risks and confidence intervals, but "[j]ust in a very straightforward way, all depending on the nature of that dataset, possibly, but possibly not. It would really all depend." *Id.* at 115. Notably, employees at her company – none of whom are statisticians or have graduate degrees in statistics – performed all of the calculations that appear in her report. *See id.* at 111, 115-16, 118.

While Dr. Kramer considers herself an expert in post-marketing adverse event reports, she never has submitted one to a pharmaceutical company or to the FDA. *See id.* at 131-33. FDA never has asked for her expertise in analyzing post-marketing adverse event reports, and she cannot recall whether she ever has published anything in the peer-reviewed medical literature about post-marketing adverse event reports. *See id.* at 133.

II. DR. KRAMER'S CAUSATION OPINIONS

Dr. Kramer submitted a 246-page expert report and a 43-page rebuttal report, in which she offers the opinion that "exposure to varenicline [the generic name for Chantix] is causally associated with increased risks of adverse neuropsychiatric events," including suicide-, depression-, and aggression-related events. Kramer Rep. at 19; *see* Rebuttal Report of Dr. Shira Kramer ("Kramer Rebuttal Rep."), at 4 (Ex. 12).

A. Dr. Kramer Admits She Employs a "Subjective" Methodology.

For this litigation, Dr. Kramer disregards the hierarchy of evidence and treats all lines of evidence as if they were equal. She admits that her analysis is not rooted in any "specific weighting or ranking scheme." Kramer Rep. at 9; Kramer Rebuttal Rep. at 6; *see* Kramer Dep. at 154. While she claims she used a "weight of the evidence" methodology, she concedes that "determinations about the weight of evidence are *subjective interpretations of 'reality'* implied by various lines of scientific evidence." Kramer Rep. at 9 (emphasis added); Kramer Rebuttal Rep. at 6. Dr. Kramer also acknowledges that her approach has "no 'hard and fast' rules for determining causation" and that every scientist employing her method brings a "unique set" of experiences, training, expertise, and value judgments, which can result in different conclusions. Kramer Rep. at 10-11.

B. Dr. Kramer Ignores the Principle of Statistical Significance and Cherry-Picks Data from Controlled Clinical Trials and Observational Studies.

Dr. Kramer has written that in any study with a control group, "The first question to ask about a difference between groups in frequency of disease is whether it is statistically significant. If it is not, the problem may either be dismissed or pursued further through studies on a larger sample." MAUSNER & KRAMER, EPIDEMIOLOGY: AN INTRODUCTORY TEXT 181 (2d ed. 1985) (Ex. 93).

While Dr. Kramer has not published an article in a peer-reviewed medical journal in more than 20 years, *see* Kramer CV at 4 (Ex. 27); Kramer Dep. at 131, in the articles she has published, she always reports the statistical significance of her findings and interprets those results differently depending on whether they are statistically significant. *See* Kramer Dep. at 276, 298-99, 304-05, 309, 313-16; Kramer et al., J. NAT'L. CANCER INST. 1987;78(5):797-804, at 801 (Ex. 91); Bunin & Kramer et al., CANCER RES. 1989;49:725-29, at 726-27 (Ex. 67); Bunin & Kramer et al., CANCER RES. 1987;47:2972-77, at 2973-75 (Ex. 66). In fact, outside of litigation, Dr. Kramer is unable to recall a single instance in which she declared a drug effect in the absence of a statistically significant result. *See* Kramer Dep. at 234-35.

Here, however, Dr. Kramer abandons the principle of statistical significance. *See* Kramer Rebuttal Rep. at 15-19; Kramer Dep. at 254 ("[I]t's not one of the

primary questions I would ask.").[1] In her report, she regularly interprets any risk ratio greater than 1.0 as evidence of increased risk, *see*, *e.g.*, Kramer Rep. at 41, 43, 46-49, even though such results do not reliably rule out that there is no true difference in risk. *See* Kramer Dep. at 388-89, 391-92.

1. Dr. Kramer Cherry-Picks Data from Controlled Clinical Trials.

In her expert report, Dr. Kramer does not analyze the overall results for suicide-related events, admitting only that there were no "statistical excesses" of such events. *See* Kramer Rep. at 39. Rather, she cites a handful of suicide-related events experienced by patients taking Chantix in individual trials, while ignoring a similar number of events that occurred – at higher counts – in patients taking placebo pills. *See id.* at 38-39; Pfizer's Intro. & Statement of Facts Relevant to All *Daubert* Motions ("SOF") § III.A.1. She also overlooks the conclusions of the European Medicines Agency ("EMA"), which scrutinized the available clinical trial data and determined, "[T]he current evidence does not support a causal link between use of varenicline and a [sic] increased risk of [suicide-related events]." CHMP Final Assessment Report, Jan. 22, 2009, at 10 (Ex. 55).

[1] While she claims that her views on significance testing have evolved, she never has submitted a paper to that effect and never has retracted her earlier work. *See* Kramer Dep. at 278-79.

For depression-related events, Dr. Kramer claims that "varenicline-treated groups have been shown to be at *consistently higher risk* for depression and depression-related events in individual clinical trials." Kramer Rep. at 54 (emphasis added). To support this claim, however, Dr. Kramer describes only those clinical trials in which patients taking Chantix experienced a higher rate of depression-related events – even though none of the results she cites is statistically significant – while saying nothing about the trials that showed a *lower* rate of such events. *See id.* at 46-49; SOF § III.A.2 (noting that half of the trials had lower rates of depression-related events in patients taking Chantix or no events at all).

After submitting her reports, Dr. Kramer identified only one trial – among the 16 Pfizer placebo-controlled trials available today – that shows a statistically significant increase in the rate of depression-related events – the A3051036 trial (Jorenby 2006). *See* Kramer Dep. at 490; Kramer Dep., Ex. 9, tab 12, *Statistically Significant Findings in Varenicline Studies* ("Kramer Table") (Ex. 42). But she did not perform statistical analyses for each trial, *see id.* at 125-48, 204-19, including one that shows a statistically significant *decrease* in depression-related events in patients taking Chantix. *See* SOF § III.A.2. Dr. Kramer also ignores data that is inconsistent with her opinion regarding the A3051036 trial, including data showing that: (1) smokers in that trial experienced significantly *fewer* depressive symptoms than smokers trying to quit cold turkey; (2) the A3051036 trial and

others comparing Chantix to Zyban showed that patients taking Chantix experienced *lower* rates of depression-related events than those taking Zyban, even though Zyban is approved as an antidepressant; and (3) an identical trial did not show an increased risk, which means the A3051036 trial's depression results were not replicated. *See* SOF § III.A.2.

Dr. Kramer also concludes that pooled analyses of Pfizer-sponsored clinical trials "have demonstrated that varenicline-exposed participants experienced higher risks" for depression-related events compared to those taking placebo. Kramer Rep. at 41. In drawing that conclusion, she did not perform any statistical analysis of the totality of evidence available from 16 placebo-controlled trials that have been completed as of today. *See* Kramer Dep. at 360, 364. Instead, she relies on an older analysis that includes only 10 trials, even though the authors of that analysis correctly concluded that "psychiatric adverse events were rare and were not significantly associated with varenicline use." Tonstad et al., DRUG SAFETY 2010;33:289-301, at 299 ("Tonstad 2010") (Ex. 118).[2] Dr. Kramer also ignores more recent meta-analyses, such as those published by the Cochrane Collaboration,

[2] Dr. Kramer also cites the data compilations from 2005 on which Dr. Olmstead bases his statistical analysis, which combined uncontrolled data with controlled data and involved even fewer trials than the Tonstad 2010 meta-analysis. *See* Kramer Rep. at 80-85. Dr. Kramer could not recall how Pfizer counted events from the open-label A3051035 trial in those compilations. *See* Kramer Dep. at 334; *see also* SOF § III.A.2.

in which the authors concluded, "There is little evidence from controlled studies of any link between [Chantix] and psychiatric adverse events." Cahill et al., COCHRANE DATABASE OF SYS. REVS. 2012, Issue 4 at 14 ("Cahill 2012") (Ex. 69).[3]

Finally, while Dr. Kramer acknowledges that a dose-response relationship is an important factor to consider in assessing causal relationships, *see* Kramer Rep. at 10, she does not address whether there is any evidence that the rates of neuropsychiatric events increase as the dose of Chantix increases. *See id., passim.*

2. Dr. Kramer Cherry-Picks Data from Controlled Observational Studies.

As with her approach to controlled clinical trials, Dr. Kramer cherry-picks results from the available observational studies and ignores the principle of statistical significance. For example, for suicide-related events, the only controlled observational study she identifies is the one conducted by the U.K.'s Medicines & Healthcare Products Regulatory Agency ("MHRA"). Even though the study authors concluded that there was no significant difference and thus "no clear evidence" that Chantix was associated with an increased risk of self-harm, Gunnell et al., BRIT. MED. J. 2009;339:b3805, at 1 ("Gunnell") (Ex. 84), Dr. Kramer interprets the non-significant, numeric differences in the study as showing an

[3] Dr. Kramer's analysis of aggression-related events follows a similar pattern; she identifies a handful of events in a selective fragment of individual trials, *see* Kramer Rep. at 56-59, even attributing importance to single events. *See id.* at 57 (describing disturbance in behavior result in Tashkin trial).

elevated risk of self-harm and suicidal thoughts. *See* Kramer Rep. at 37. Dr. Kramer likewise does not address other study findings at odds with her conclusion such as MHRA's analysis showing that patients taking Chantix had a *lower* relative risk of depression, as measured by the initiation of antidepressant therapy, than those taking NRT – a difference that was very nearly statistically significant. *See id*. at 37 (mentioning only the self-harm and suicidal ideation results); *id.* at 41-54 (omitting Gunnell entirely in the portion of her report addressing depression-related events); *id.* at 180 (listing the depression result but including no explanation of its significance).

After Pfizer's experts pointed out her failure to reconcile the depression results with her causation opinion, Dr. Kramer criticized the MHRA authors' definition of depression. *See* Kramer Rebuttal Rep. at 26. Even in her rebuttal report, she does not explain how the reduced risk of depression seen in that study is consistent with her causation opinion, offering only a blanket statement that she "considered the weight of the evidence regarding each of the relevant neuropsychiatric outcomes, including depression, rather than basing my conclusions on any individual study or data point." *Id.*

Similarly, in her original report, Dr. Kramer provides no explanation for how her "weight of the evidence" review accounted for the two large, FDA-sponsored observational studies, which found no difference in the risk of

neuropsychiatric hospitalizations for smokers taking Chantix compared to those using the nicotine patch. *See* Kramer Rep. at 188; FDA Drug Safety Communication, Oct. 24, 2011, at 1 (Ex. 135). Again, after Pfizer's experts pointed out her oversight, she questioned the utility of measuring neuropsychiatric hospitalizations and said that FDA studies were not peer-reviewed. *See* Kramer Rebuttal Rep. at 30.

While she overlooks the Gunnell depression results and FDA-sponsored studies, Dr. Kramer relies on a single, small controlled observational study in support of her opinion on depression-related events. *See* Kramer Rep. at 47 (citing Stapleton et al., ADDICTION 2007;103:146-54, at 146 ("Stapleton") (Ex. 114)); Kramer Table at 2 (identifying "Stapleton 2008 [sic]").[4] That study, which consisted of only 412 patients, compared the effectiveness of Chantix to the nicotine patch. While Chantix patients reported more events of "low mood / depression" than those using the nicotine patch, the number of events was small and was not adjusted for the possible confounding effect of nicotine withdrawal.

[4] Of the cohort studies listed in the Kramer Table, neither the Campbell 2010 study nor the Cornelius 2010 abstract had a control group. *See* Campbell & Anderson, AM. J. HEALTH-SYS PHARM. 2010;67:1832-37, at 1835 ("Campbell") (Ex. 70); Cornelius et al., DRUG SAFETY 2010;33:904-05, at 904 ("Cornelius") (Ex. 72); Deposition of Dr. Jon Wesley Boyd, Mar. 6, 2012, at 229-30 ("Boyd Dep.") (Ex. 31); Kramer Dep. at 447-51, 454. The other observational study data cited in Dr. Kramer's report consists of uncontrolled studies or post-marketing surveillance data. *See* Kramer Table at 3; SOF App., Fig. 9 & 10.

See Stapleton at 150-51. Dr. Kramer again reaches conclusions that are at odds with the conclusions of the study's authors, who observed that "[t]here was no evidence of a difference in experience of adverse mood" and "[t]here was no evidence that varenicline exacerbated mental illness." *Id.* at 146, 150-51; *see id.* at 150-51 (noting "there was little evidence that when experienced, the severity of symptoms were different in the two cohorts"). Dr. Kramer does not identify any other controlled observational study that supports her causation opinion on suicide or depression.

C. Dr. Kramer Relies on Data from Uncontrolled Studies and Post-Marketing Adverse Event Reports.

While Dr. Kramer admits that an uncontrolled study does not enable researchers to compare the incidence of an adverse event in patients taking a medication to the incidence in those not taking the medication, *see* Kramer Dep. at 165-68, she relies extensively on data from uncontrolled studies and post-marketing adverse event reports (including disproportionality analyses, prescription event monitoring studies, case series, and case reports) as the basis of her causation opinion.

Uncontrolled studies. For example, Dr. Kramer relies on the uncontrolled Campbell observational study, which analyzed the rate of mental health encounters in 78 veterans taking Chantix for smoking cessation. *See* Kramer Rep. at 38, 50 (citing Campbell); Campbell at 1832. The authors found that those patients had

more mental health encounters while on Chantix than prior to starting therapy, but there was no control group of smokers who were trying to quit without Chantix. *See* Campbell at 1832; Boyd Dep. at 229-30; Kramer Dep. at 451, 454. As a result, there was no way to know whether the number of mental health encounters was higher than, the same as, or lower than what one might observe in smokers trying to quit cold turkey. As the authors acknowledged, "the lack of a control group . . . makes interpreting the clinical relevance [of the study] difficult." Campbell at 1835-36.

The authors also noted that they had limited "ability to evaluate other possible causes of [mental health] decompensation (e.g., psychosocial stressors)." *Id*. at 1835. Further, more than half of the veterans had a concomitant mental illness, which "alone necessitates an increase in provider follow-up." *Id*. As a result, the authors cautioned that the increase in mental health encounters "does not necessarily mean that this subpopulation is more susceptible to neuropsychiatric effects of varenicline." *Id.* at 1835-36. Moreover, while Dr. Kramer points to two cases of suicidal ideation, *see* Kramer Rep. at 38, she fails to note that Chantix was not found to be a factor in those cases. *See* Campbell at 1834.

Dr. Kramer also cites an uncontrolled clinical trial by McClure et al. for the proposition that patients with a history of psychiatric illness were more likely to experience depression than patients without such a history. *See* Kramer Rep. at 51-

52 (citing McClure et al., J. SUB. ABUSE TREAT. 2010;38:394-402, at 398 ("McClure 2010") (Ex. 95); McClure et al., J. GEN. INTERN. MED. 2009;24(5):563-69, at 566 ("McClure 2009") (Ex. 94)). In that trial, every patient took Chantix, but the smokers received different forms of behavioral therapy; as a result, there was no control group of smokers trying to quit without taking Chantix. *See* McClure 2009 at 564; McClure 2010 at 395-96. Moreover, the study showed no significant difference in rates of change in depression and stress scores between those with a past history of a major depressive disorder and those without a history of depression. *See* McClure 2009 at 565. In fact, depression and stress scores *declined* in both groups – in other words, all patients experienced *less* depression while taking Chantix. *See id*. at 566 (Figure 1).

Post-marketing adverse event reports. In her report, Dr. Kramer cites various examples of post-marketing adverse event reports, none of which support an association between Chantix and neuropsychiatric events. For example, Dr. Kramer cites disproportionality analyses from databases such as FDA's Adverse Event Reporting System ("AERS"). *See* Kramer Rep. at 31-35, 41, 51. As Dr. Kramer admits, however, such analyses only measure the proportion of a specific type of adverse event reported for a medication against the total number of events reported for that medication, and compare that proportion to other

medications – they do not measure the respective incidence rates of the adverse event in populations of a known size. *See* Kramer Dep. at 135-37.

Dr. Kramer also cites a number of prescription event monitoring studies – which are surveys sent in the mail to physicians who prescribed Chantix to their patients, rather than studies based on a review of medical records. *See* Kramer Rep. at 37-38, 49-50 (citing Harrison-Woolrych et al., DRUG SAFETY 2011;34:763-72, at 763 ("Harrison-Woolrych") (Ex. 86); Kasliwal et al., DRUG SAFETY 2009;32(6):499-507, at 500 ("Kasliwal") (Ex. 89); Cornelius at 904. Dr. Kramer concedes, however, that prescription event monitoring studies do not have a control group, so the researchers cannot compare the rates of adverse events in smokers taking Chantix to the rates in smokers trying to quit without Chantix. *See* Kramer Dep. at 447-51; Harrison-Woolrych at 767; Kasliwal at 500; Cornelius at 904.

Finally, Dr. Kramer cites a number of case series, case reports, and compilations of individual adverse event reports, including those she claims demonstrate what is known as challenge / dechallenge / rechallenge.[5] *See* Kramer

[5] Dr. Kramer defines "positive dechallenge" as a "'partial or complete disappearance of an adverse experience after withdrawal of the suspect product.'" Kramer Rep. at 3 (quoting FDA, GUIDANCE FOR INDUSTRY – POSTMARKETING SAFETY REPORTING FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS INCLUDING VACCINES, DRAFT GUIDANCE (2001) ("FDA 2001") (Ex. 127)). She defines "positive rechallenge" as the "'reoccurrence of similar signs and symptoms upon reintroduction of the suspect product.'" Kramer Rep. at 3 (quoting FDA 2001).

Rep. at 36, 51-53, App. Table A6. Dr. Kramer contends that evidence of a positive dechallenge or rechallenge "is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event." Kramer Rep. at 3 (citing FDA, GUIDANCE FOR INDUSTRY – GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT (Mar. 2005) ("FDA PHARMACOVIGILANCE GUIDANCE") (Ex. 128)); *see* Kramer Rep. at 18.

In contrast to Dr. Kramer's interpretation, FDA observed only that a "single well-documented case report can be viewed as a *signal*, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use." FDA PHARMACOVIGILANCE GUIDANCE at 4 (emphasis added). According to FDA, a signal merely indicates "the need for further investigation, *which may or may not lead to the conclusion that the product caused the event*. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken." *Id.* at 4 (emphasis added). At most, according to FDA, reports of dechallenge and rechallenge "*may* suggest a causal relationship," *id.* at 6, but "[c]onfounded cases are common, especially among patients with complicated medical conditions . . . . For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product." *Id*. at 7. Such confounding is especially inherent for psychiatric symptoms because these

symptoms appear "coincidental with [medication] use." Wysowski et al., J. AM. ACAD. DEMATOL. 2001;45:515-19, at 518 (Ex. 122).

Dr. Kramer's claim also is inconsistent with FDA's analyses of the Chantix dechallenge / rechallenge data. FDA found that Chantix had a *lower* proportion of suicide (attempt or completed) and self-injurious events than Zyban or the nicotine patch, and that the proportion of dechallenge for the patch and Chantix were similar. *See* Pollock et al., FDA Office of Surveillance and Epidemiology, *Suicidality*, July 16, 2008, at 3 ("FDA AERS Suicide Analysis") (Ex. 52); *see* SOF § III.C. While FDA stated that the data suggested a "possible association," it did not conclude that Chantix causes serious neuropsychiatric events. *See* FDA AERS Suicide Analysis at 43. Instead, FDA requested a more rigorous clinical trial, which is currently underway, *see* SOF § III.A.4, and sponsored two large observational studies, which showed no increased risk of serious neuropsychiatric events. *See id*. at SOF § III.B.

D. Dr. Kramer Relies on Statements from Regulatory Authorities, Even Though None of Them Say that Chantix Causes Serious Neuropsychiatric Events.

Dr. Kramer also relies on a collection of statements from regulatory agencies to support her causation opinion. *See* Kramer Rep. at 70-73. She does not reconcile that claim with the conclusions of the EMA, which determined that "the current evidence does not support a causal link between use of varenicline and a

[sic] increased risk of [suicide-related events]." CHMP Final Assessment Report, Jan. 22, 2009, at 10. Nor does she address the language in the current FDA-approved label, which notes that while serious neuropsychiatric events have been "reported" in patients taking Chantix, such reports are not sufficient to establish a causal relationship to Chantix. *See* SOF § I.F. FDA never has stated that Chantix causes serious neuropsychiatric events, but rather has requested that Pfizer conduct a large clinical trial (now ongoing) to investigate this very issue.

III. DR. KRAMER'S OPINIONS ON ISSUES OTHER THAN CAUSATION

Dr. Kramer also offers opinions regarding what Pfizer knew at certain points in time based on company e-mails and internal documents made available to her by Plaintiffs' counsel. *See* Kramer Rep. at 79-121; Kramer Dep. at 499-501. Based on those documents, Dr. Kramer opines that Pfizer knew as early as 2005 that Chantix increases the risk of neuropsychiatric events, but did not do enough to warn the public of these risks, did not design studies to adequately evaluate these risks, and failed to collect adequate information on adverse event reports. *See* Kramer Rep. at 79-121. Dr. Kramer admits, however, that she has no expertise in determining a corporation's state of mind and that her method for determining what Pfizer allegedly knew has no error rate. *See* Kramer Dep. at 497, 502-04.

Further, while Dr. Kramer's report does not contain any opinions about the adequacy of the Chantix label, she testified that her opinions "will probably relate

to the issue of the adequacy of the labeling with regard to the occurrence, the risk of neuropsychiatric adverse events and when the public should have been warned." *Id.* at 506. However, Dr. Kramer never has drafted a label for a pharmaceutical product, worked at FDA, or been asked by FDA to review a label. *See id.* at 145-46. She also has no training related to FDA labeling regulations. *See id.* at 508.

ARGUMENT

The Court should preclude Dr. Kramer from offering a general causation opinion. First, she lacks a reliable basis to opine that there is a statistically valid association between the use of Chantix and serious neuropsychiatric events. Much of the data on which she relies is uncontrolled, and the overwhelming majority of the controlled data she cites are not statistically significant and thus are not within the error rate that is generally accepted by the medical community.

Second, Dr. Kramer lacks a reliable basis to conclude that any statistical association reflects a causal relationship. She relies on only a selective fragment of the available data to support her opinion – thereby ignoring the principles of replication and consistency. She also fails to consider the lack of a dose-response relationship.

Finally, the Court also should exclude her opinions about what Pfizer knew or the adequacy of the Chantix labels.

I. THE COURT SHOULD EXCLUDE DR. KRAMER'S GENERAL CAUSATION OPINION

A. Dr. Kramer Lacks a Reliable Basis to Conclude that There Is a Valid Statistical Association Between the Use of Chantix and Serious Neuropsychiatric Events.

To support an opinion that Chantix causes serious neuropsychiatric events, Dr. Kramer first must provide a reliable basis to conclude that there is a valid statistical association between the use of Chantix and such events. For the reasons outlined below, she has failed to do so.

1. Dr. Kramer Bases Much of Her Opinion on Uncontrolled Data, Which Cannot Establish a Statistical Association.

The Court should exclude Dr. Kramer's opinions because she relies extensively on uncontrolled data, including post-marketing adverse event reports. As the Eleventh Circuit has observed, "A reliable methodology should take into account the background risk." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005). Without a control group to account for the background risk of an adverse event of interest, researchers cannot "rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors." *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002). Thus, "[u]ncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation." *McClain*, 401 F.3d at 1250; *see id.* at 1243-44, 1253-54 (reversing a

district court for abuse of discretion when it failed to exclude experts who relied on uncontrolled data); *Hendrix ex rel. G.P. v. Evenflo Co.*, 609 F.3d 1183, 1197 (11th Cir. 2010) (noting that uncontrolled data such as adverse event reports and case reports alone are "insufficient to show general causation"); *Rider*, 295 F.3d at 1199 (calling case reports "merely accounts of medical events" that "reflect only reported data, not scientific methodology"); *see also* Pfizer's Mem. of Ps & As in Support of its Mot. to Exclude Certain Opinions of Dr. Richard E. Olmstead ("Olmstead Br." or "Olmstead Brief"), Arg. § I.A; Pfizer's Mem. of Ps & As in Support of its Mot. to Exclude Certain Opinions of Dr. Curt Furberg ("Furberg Br." or "Furberg Brief"), SOF § II.B.

Here, because suicide and depression-related events occur regularly among people not taking Chantix – and at even higher rates among smokers trying to quit – a control group is needed to determine whether the rates of such events in patients taking Chantix are distinguishable from the rates in smokers trying to quit without Chantix. *See* Kramer Dep. at 165-68. Because she relies extensively on uncontrolled data such as post-marketing adverse event reports, her methodology is unreliable, and the Court should exclude her causation opinion. *See* Olmstead Br., Arg. § I.A; Furberg Br., SOF § II.B.

Dr. Kramer claims that a handful of adverse events demonstrate dechallenge and rechallenge, and therefore are sufficient to support her causation opinion. This

claim is at odds with FDA's interpretation of the dechallenge / rechallenge data, which found a "possible association," but not causation. *See* FDA AERS Suicide Analysis at 43. In addition, the FDA Guidance on which she relies does not support her opinion, as it says only that an individual episode of dechallenge and rechallenge may constitute a signal requiring further investigation – not that such a report constitutes sufficiently reliable evidence to conclude that a medication causes an adverse event that occurs commonly in patients not taking the medication at issue.

Moreover, as the Eleventh Circuit has noted, "dechallenge / rechallenge tests are still case reports and do not purport to offer definitive conclusions as to causation." *Rider*, 295 F.3d at 1200. The mere temporal connection between exposure and the onset of symptoms is entitled to "'little weight in determining causation.' . . . It is also subject to the problem of assuming what the witness is trying to prove. This pitfall will most likely arise when, as here, there are not scientific controls in place." *McClain*, 401 F.3d at 1254 (quoting *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 278 (5th Cir. 1998)).

Given that serious neuropsychiatric events occur regularly in smokers trying to quit without medication, the presence of a few anecdotal, uncontrolled reports of dechallenge / rechallenge cannot provide a reliable foundation for Dr. Kramer's opinion.

2. Even Where Dr. Kramer Relies on Controlled Data, She Ignores the Importance of Statistical Significance.

In those instances where Dr. Kramer does rely on controlled data, she still lacks a reliable basis to conclude that there is a valid statistical association between Chantix and serious neuropsychiatric events. Dr. Kramer consistently ignores the error rate of her methodology because she does not consider the statistical significance of the results she analyzes. Unless an adverse event is of a type that almost never occurs in the background population, a valid statistical association between exposure to a medication and the event of interest must be established before concluding that the medication caused the adverse event. *See* SOF §§ II.A.4, II.B.

Statistical significance – whether expressed as a p-value below the generally accepted threshold of 0.05 or a 95% confidence interval that does not include a risk ratio of 1.0 – ensures that an observed association is not due to the play of chance. *See* SOF § II.B.2. Because statistical significance helps identify the error rate or probability of a false positive result, Plaintiffs' experts – including Dr. Kramer – acknowledge the role of significance testing in their work outside of litigation, routinely report the statistical significance of their findings when they publish papers in the peer-reviewed medical literature, and interpret results much differently depending on whether or not they are statistically significant. *See id.* (describing Dr. Kramer's use of statistical significance outside of litigation).

Dr. Kramer, however, dismisses statistical significance in interpreting the Chantix data. Instead, she claims – after being criticized by Pfizer's experts – that a "substantial body of literature . . . argues against reliance upon arbitrary p-values and statistical significance testing in assessing the validity of findings." Kramer Rebuttal Rep. at 17. Yet in her report, she cites only a handful of articles – some of which were not published in the peer-reviewed medical literature – and even the excerpts she selects characterize significance testing as "commonly used" and "ingrained." *Id.*

Dr. Kramer also cites *Matrixx Initiatives, Inc. v. Siracusano*, 131 S.Ct. 1309 (Mar. 22, 2011), a case involving allegations of securities fraud, to support her claim that statistically significant results are not required to support a finding of causation. *See* Kramer Rebuttal Rep. at 18. At issue in that case was whether the failure to disclose adverse event reports could constitute a material omission under securities laws. In that context, the Supreme Court observed that statistically significant epidemiological evidence is not "the only reliable indication of causation," in part because "[s]tatistically significant data are not always available." 131 S.Ct. at 1312, 1319. For example, an adverse event may be "subtle or rare," *id.* at 1319, such as the adverse event at issue in *Matrixx* – a sudden loss of smell known as anosmia, which had been reported in a small number of patients and which had not occurred even once in any clinical trial of

the medication or in any controlled observational study. *See id.* at 1315-16. Under those circumstances, the Court noted, a "lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events." *Id.* at 1319.[6]

The Court limited its holding, however, by noting that "we do not attempt to define here what constitutes reliable evidence of causation." *Id*. That statistically significant results are not always required to prove causation "is not to say that statistical significance (or the lack thereof) is irrelevant – only that it is not dispositive of every case." *Id.* at 1321. The Court also remarked that non-significant data such as adverse event reports could prompt action by FDA, which "sometimes acts on the basis of evidence that suggests, but does not prove, causation." *Id.* at 1320; *see id.* (noting that "FDA may make regulatory decisions against drugs based on postmarketing evidence that gives rise to only a suspicion of causation.").

Thus, in the context of a securities fraud suit, in which the Supreme Court had to assume the plaintiffs' allegations were true, a reasonable investor might

[6] Courts in the Eleventh Circuit have made similar comments, noting that the lack of epidemiological data "is not fatal to a plaintiff's case," *Rider*, 295 F.3d at 1198, but makes an expert's "task to show general causation more difficult," *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1337 (11th Cir. 2010), and "raises the question of whether the causation opinions of [the] experts are merely speculative and not based on scientific knowledge." *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001).

regard non-significant results related to an adverse event that rarely occurs in the background population as "material" and affecting the "total mix" of information, *id.* at 1322 – which is a far cry from the *Daubert* context, in which a court must perform a gatekeeping role to ensure that evidence of causation is reliable and relevant.

Indeed, in light of *Daubert's* focus on the error rate associated with an expert's method, *see Daubert v. Merrill Dow Pharms., Inc.*, 509 U.S. 579, 594 (1993), courts regularly exclude experts who rely on statistically non-significant results. In *General Electric Company v. Joiner*, for example, the Supreme Court found that there was "simply too great an analytical gap" between an expert's opinion and the data where one of the epidemiological studies on which he relied did not establish a statistically significant increase in risk. 522 U.S. 136, 145-46 (1997). While "statistical significance by itself . . . should not mechanically control whether an epidemiological analysis is sufficiently reliable to be admissible," where an expert "places undue emphasis on statistically insignificant evidence," as Dr. Kramer does here, "it may indicate that the expert's methods are unreliable." *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 892 (E.D. Ark. 2010). As one court in the Eleventh Circuit put it, an expert "cannot lump

together lots of hollow evidence in an attempt to determine what caused a medical harm." *Siharath*, 131 F. Supp. 2d at 1371.[7]

Plaintiffs may cite *In re Neurontin Marketing, Sales Practices, & Products Liability Litigation*, 612 F. Supp. 2d 116 (D. Mass. 2009), to support Dr. Kramer's views. There, the court found that an FDA-sponsored meta-analysis of 199 clinical trials evaluating more than 43,000 patients who took an anti-epileptic drug ("AED") established a statistically significant increase in the risk of suicide-related behavior for the class of medications as a whole and for the subset of AEDs to which Neurontin belonged, even though the Neurontin data were not statistically significant. *See In re Neurontin*, 612 F. Supp. 2d at 134-35, 138, 140. The court also noted that: (1) FDA officials had stated publicly that FDA was "*unequivocally comfortable* with . . . saying that [the FDA meta-analysis] establishes causality" for the class; and (2) the Neurontin label indicates that AEDs, including Neurontin, "*increase the risk* of suicidal thoughts or behavior . . . ." *Id.* at 135-36 (emphasis added).

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[7] *See also, e.g.*, *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996); *Brock v. Merrell Dow Pharms., Inc.*, 874 F.2d 307, 309 (5th Cir. 1989), *modified*, 884 F.2d 166, 167 (5th Cir. 1989); *Smith v. Wyeth-Ayerst Labs. Co.*, 278 F. Supp. 2d 684, 691 (W.D.N.C. 2003); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 533 (W.D. Pa. 2003); *In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 830-31 (E.D. Tex. 2002); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1032, 1034 (S.D. Ill. 2001); *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995).

In evaluating the epidemiological data, the court observed, "While an epidemiological study is not *per se* required, establishing general causation without some 'confirmatory' evidence of an association between the drug and the negative effect can be an uphill battle." *Id.* at 132. The court acknowledged that "[s]tatistical significance is one of the factors the Court should examine when determining whether a drug can cause an adverse event." *Id.* at 140 (citing *Daubert*, 509 U.S. at 594). "Drug-specific statistical significance, though, is not always required where it is not reasonably attainable." *Id.* In light of the large, FDA-sponsored meta-analysis of the class of AEDs and definitive statements from FDA, the court found that there was sufficient evidence of a statistical association to consider causation factors such as replication and consistency, dose response, and biological plausibility. *See id.* at 158.

Here, the Chantix data differs from *Neurontin* in two important respects. First, this is not an instance in which "[d]rug-specific statistical significance . . . is not reasonably attainable" and a class-wide meta-analysis demonstrates a statistical association. *Id.* at 140. Rather, meta-analyses of the Chantix clinical trial data, the results of individual clinical trials, and large observational studies sponsored by regulatory agencies show *no* reliable evidence of an increased risk of suicide or depression-related events. Second, unlike in *Neurontin*, where FDA stated that it was "unequivocally comfortable" concluding that there was a causal relationship,

FDA never has said that Chantix causes or increases the risk of events such as suicide or depression. *Id*. at 35.

Where, as here, an event occurs frequently in the general population, the medical and scientific communities rely on statistical significance to assess whether the risk in patients taking a medication is truly distinguishable from the risk already inherent in the background population. That is why every peer-reviewed analysis of the Chantix clinical trial and controlled observational study data uses conventional statistical significance thresholds to evaluate the reliability of the results. Without statistical significance as an objective, established criteria to evaluate the probability that an observed difference is due to the play of chance, researchers would have no way to test the error rate of their results and would instead have to resort to Dr. Kramer's "subjective" methodology. *See Daubert*, 509 U.S. at 590. Dr. Kramer's extensive reliance on non-significant results makes her methodology inherently unreliable, and the Court should exclude her causation opinion as a result.

B. Dr. Kramer Lacks a Reliable Basis to Conclude that Chantix Causes Serious Neuropsychiatric Events.

Even if Dr. Kramer were able to establish a valid statistical association, she still lacks a reliable basis to conclude that Chantix causes serious neuropsychiatric events. She cherry-picks data that supports her conclusions, while ignoring the great weight of epidemiological evidence that is contrary to her opinions. She also

fails to consider the principle of dose response. Finally, the regulatory statements she cites do not support her causation opinion and are not proper under Eleventh Circuit law. As a result, the Court should exclude her causation opinion in its entirety.

1. Dr. Kramer Ignores the Principles of Replication and Consistency and Instead Cherry-Picks Only the Results that Support Her Opinions.

The Court should exclude Dr. Kramer's causation opinion because she ignores the principles of replication and consistency and instead cherry-picks only those studies that are "out of sync with the conclusions in the overwhelming majority of the epidemiological studies." *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (11th Cir. 1999). Where an expert relies on a selective fragment of the available data to support her opinion, she has not employed a reliable methodology and should be excluded under Fed. R. Evid. 702. *See* Olmstead Br., Arg. § II.A.

Randomized, double-blind clinical trials. With respect to clinical trial data regarding suicide-related events, Dr. Kramer "simply ignore[s] the epidemiology that exists" by omitting any reference to the overall results – which showed *lower* event counts in patients taking Chantix compared to those quitting without medication – which is not a "reliable scientific approach." *Perry v. Novartis Pharms. Corp*., 564 F. Supp. 2d 452, 465-66 (E.D. Pa. 2008). She also "selectively chose [her] support from the scientific landscape" by summarizing

only the events that occurred in patients taking Chantix, while overlooking similar events that occurred more often in patients taking placebo. *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2004) (quoting *Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999)).

Dr. Kramer engages in a similarly flawed method for depression-related events. She cites outdated fragments of pooled data, even though she "was aware of a body of published medical and scientific literature, including controlled clinical trials," which were completed after those outdated compilations were prepared. *Rimbert v. Eli Lilly & Co.*, No. CIV 06-0874, 2009 WL 2208570, at *14 (D.N.M. July 21, 2009). She also "ignore[s] or discount[s] without explanation" the totality of data available today, which shows no difference in the rates of such events. *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 885 (10th Cir. 2005); *see In re Bextra & Celebrex Mktg. Sales Practices & Prods. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007). As the Eleventh Circuit explained, scientists do not "leap to specific conclusions about causation or toxicity from incomplete evidence," *McClain*, 401 F.3d at 1248, which is exactly what Dr. Kramer did in failing to consider the totality of clinical trial data.

Rather, Dr. Kramer discusses only trials with higher rates of depression-related events and one trial with a statistically significant difference, while failing to explain the trials that showed lower rates, including one with a statistically

significant *decrease* in risk. In doing so, Dr. Kramer engages in a "selective use of facts [that] fails to satisfy the scientific method of *Daubert*." *Barber v. United Airlines*, 17 F. App'x 433, 437 (7th Cir. 2001).

Dr. Kramer also disregards the analysis conducted by European regulators, who scrutinized the same controlled clinical trial data and determined that "the current evidence does not support a causal link" between the use of Chantix and suicide-related events. CHMP Final Assessment Rep. at 10. This finding is consistent with the finding of the independent Cochrane Collaboration, which found "little evidence" of a link between Chantix and neuropsychiatric events. Cahill 2012 at 14. Finally, Dr. Kramer ignores the ongoing trials that Pfizer is performing at the request of EMA and FDA, which ethically could not be performed if it were established that Chantix causes serious neuropsychiatric events. *See* SOF § III.A.4.

Controlled observational studies. Dr. Kramer's approach to observational study data follows the same pattern. In the MHRA study, she relies on non-significant results for self-harm and suicidal thoughts, even though the MHRA concluded that their study showed no "clear evidence" of an association between suicide-related behavior and the use of Chantix. Gunnell at 1. The Eleventh Circuit is skeptical of experts who employ such methods, as an expert who "draws unauthorized conclusions from limited data – conclusions the authors of the study

do not make" – shows a "lack of scientific rigor." *McClain*, 401 F.3d at 1248; *see Joiner*, 522 U.S. at 145. As a result, "[i]t is axiomatic that causation testimony is inadmissible if an expert relies upon studies or publications, the authors of which were themselves unwilling to conclude that causation had been proven." *Huss v. Gayden*, 571 F.3d 442, 459 (5th Cir. 2009).

Dr. Kramer's original report also makes no attempt to reconcile the *lower* rate of depression among patients taking Chantix compared to the nicotine patch in the MHRA study with her opinions on suicide and depression. It was only after Pfizer's experts noted her failure to explain that data that she questioned certain aspects of the study, a sequence the court should find "troubling." *Haller v. AstraZeneca Pharms. LP*, 598 F. Supp. 2d 1271, 1296-97 (M.D. Fla. 2009) (finding it "troubling . . . that the underpinnings of [the expert's] opinions have changed in direct response to [defendant's] motion practice"). While she then downplays these contrary findings, she offers only her bare assertion that she considered them as part of the weight of the evidence, an *ipse dixit* that is insufficient under *Daubert*. *See Joiner*, 522 U.S. at 146.

Likewise, Dr. Kramer's first report contains no discussion of the large, FDA-sponsored observational studies, which found no difference in the risk of neuropsychiatric hospitalizations. After being challenged by Pfizer's experts, she then claims for the first time that the studies did not allow for an assessment of less

severe neuropsychiatric events, thereby "downplaying [these] contrary findings or conclusions." *In re Prempro*, 738 F. Supp. 2d at 892. Notwithstanding her belated criticisms, Dr. Kramer does not explain how the results of the FDA-sponsored studies could be consistent with her opinion that Chantix causes serious neuropsychiatric events. Instead, she relies on a much smaller sample in the Stapleton study, where she again draws conclusions that are inconsistent with those of the study authors. *See Joiner*, 522 U.S. at 145; *McClain*, 401 F.3d at 1248.

Dr. Kramer's approach – cherry-picking isolated studies or outdated fragments of data that "support [her] conclusion and rejecting or ignoring the great weight of the evidence that contradicts [her] conclusion" – is not "good science." *In re Bextra*, 524 F. Supp. 2d at 1176. She interprets studies in ways the study authors do not, identifies limitations in studies that do not support her opinion only after she fails to address the studies the first time, and even then offers only her assurance that she considered the contrary data in conducting her review of the evidence, none of which suggests a methodology grounded in "sound scientific principles." *Rider*, 295 F.3d at 1197 (citing *Kumho Tire v. Carmichael*, 526 U.S. 137, 152 (1999)). Her opinion should be excluded because there is "simply too great an analytical gap between the data and the opinion [she] proffered." *Joiner*, 522 U.S. at 146; *see Allison*, 184 F.3d at 1316; *McClain*, 401 F.3d at 1248.

2. Dr. Kramer Ignores the Lack of a Dose-Response Relationship.

Dr. Kramer also produces no evidence of a dose-response relationship – evidence that should exist if an alleged statistical association reflects an actual effect in the human body. In *McClain*, the Eleventh Circuit explained that "[d]ose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect." 401 F.3d at 1242. Dr. Kramer's failure to address whether a dose-response relationship exists "casts suspicion on the reliability of [her] methodology." *Id.* at 1241-42; *see id*. at 1241, n.6 (noting that "the link between an expert's opinions and the dose-response relationship is a key element of reliability in toxic tort cases."). Dr. Kramer's failure to consider dose further undermines the reliability of her methodology. *See* Olmstead Br., Arg. § II.B.

3. Comments by Regulatory Agencies Are Not a Reliable Foundation for Dr. Kramer's Causation Opinions.

Dr. Kramer also relies on a collection of statements from regulatory agencies. As a threshold matter, statements and conclusions of regulatory agencies are "unreliable proof of medical causation" because such regulatory agencies "employ[] a reduced standard (vis-à-vis tort liability) for gauging causation. . . ." *McClain*, 401 F.3d at 1250 (quoting *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)); *see Rider*, 295 F.3d at 1201 (noting that regulatory

agencies like FDA employ "a much lower standard than that which is demanded by a court of law").

As the Eleventh Circuit has explained, "[a] regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required by the *Daubert* trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable." *Rider*, 295 F.3d at 1201. Even where FDA withdraws a medication, that decision is not reliable evidence of causation. *See Matrixx*, 131 S.Ct. at 1320 (noting that FDA "sometimes acts on the basis of evidence that suggests, but does not prove, causation."); *see also Glastetter*, 252 F.3d at 991. For these reasons, Dr. Kramer's citation to statements of various regulatory agencies cannot serve as a reliable foundation for her opinion.

Relying on such statements is especially problematic here because the regulatory agencies never have stated that Chantix causes or increases the risk of serious neuropsychiatric events – only that such events have been reported or that there "may" be an association. *See* SOF §§ I.F, III.A; *Rider*, 295 F.3d at 1201 (rejecting reliance on an FDA statement and noting that the FDA did not "draw[] a conclusion about causation"). As such, Dr. Kramer has not applied her methods reliably to the facts of the case. *See* Fed. R. Evid. 702; *Daubert*, 509 U.S. at 591.

II. THE COURT SHOULD EXCLUDE DR. KRAMER'S OTHER OPINIONS

A. Dr. Kramer's Opinions About What Pfizer Knew and Its Conduct Are Not the Proper Subject of Expert Testimony.

Dr. Kramer also offers opinions about what Pfizer knew at various points in time and whether its conduct was appropriate based on that knowledge, an opinion she derives from her review of internal documents provided to her by Plaintiffs' counsel. *See* Kramer Rep. at 79-121; Kramer Dep. at 499-501. Dr. Kramer has no expertise in determining a corporation's state of mind or FDA requirements applicable to pharmaceutical companies. *See* Kramer Dep. at 497. Furthermore, these opinions are not based on any industry standards or generally accepted methods to determine what Pfizer knew or did. *See id.* at 502-04.

As noted in the Furberg Brief, opinions about what a corporation knew are not an appropriate subject of expert testimony. *See* Furberg Br., Arg. § II. That is because opinions based on inferences drawn from the review of internal company documents are not the product of any scientific method, specialized training, or knowledge under Rule 702, and "the trier of fact is entirely capable of determining whether or not to draw such conclusions without any technical assistance" from an expert. *City of Tuscaloosa v. Harcros Chems. Inc.*, 158 F.3d 548, 565 (11th Cir. 1998); *see In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 546 (S.D.N.Y. 2004). As another court in this district noted, "[T]hese opinions describe lay

matters which a jury is capable of understanding without the expert's help. . . ." *In re Trasylol Prods. Liab. Litig.*, No. 08-MD-01928, 2010 WL 4052141, at *8 (S.D. Fla. May 12, 2010). Therefore, allowing experts to testify on the basis of inference "improperly [allows them] to assume the role of advocates for the plaintiffs' case by arguing as to the intent or motives underlying the conduct of" the defendant, which *Daubert* does not permit. *In re Rezulin*, 309 F. Supp. 2d at 546. For these reasons, the Court should not allow Dr. Kramer to offer opinions about what Pfizer knew and its conduct.

B. Dr. Kramer Did Not Disclose Any Opinions About Labeling in Her Report and Is Not Qualified to Offer Such Opinions Even If She Had.

During her deposition, Dr. Kramer stated that her opinions "will probably relate to the issue of the adequacy of the labeling with regard to the occurrence, the risk of neuropsychiatric adverse events and when the public should have been warned." Kramer Dep. at 506. But nothing in the nearly 300 pages of Dr. Kramer's reports discloses an opinion that the Chantix labels were inadequate, and an expert may not offer opinions that are not adequately disclosed in advance. *See Mitchell v. Ford Motor Co*., 318 F. App'x. 821, 824-25 (11th Cir. 2009) (affirming exclusion of expert for failing to disclose the bases of an opinion).

Moreover, Dr. Kramer is not qualified to offer opinions on the adequacy of labeling. She never has drafted a label for a pharmaceutical product, never has

worked at FDA, cannot recall taking a course or attending a conference on FDA labeling regulations, and never has been asked to review a label by FDA. *See* Kramer Dep. at 146, 506-07. Even being a physician "does not qualify [one] to speak as an expert[] in the field of the requirements of the federal regulations regarding labeling and warnings for FDA approved drugs." *In re Diet Drugs*, No. MDL 1203, 2000 WL 876900, at *11-12 (E.D. Pa. June 20, 2000); *see also In re Diet Drugs*, No. MDL 1203, 2001 WL 454586, at *1 (E.D. Pa. Feb. 1, 2001) (finding physician "not qualified to offer opinions about the accuracy of labels or the appropriateness of [a pharmaceutical company's] conduct concerning its alleged failure to warn").

Here, Dr. Kramer does not even have the experience of a practicing physician, as she is not a medical doctor and never has prescribed medications herself. See Kramer Dep. at 127. Thus, even if Dr. Kramer had disclosed an opinion about the Chantix labels in her report, she is not qualified to offer any testimony on the subject.

CONCLUSION

For these reasons, the Court should exclude Dr. Kramer's causation opinions in their entirety. The Court also should preclude Dr. Kramer from testifying that

Pfizer knew Chantix caused serious neuropsychiatric events or that the label for Chantix was inadequate.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on May 18, 2012, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF system which will send notification to the attorneys of record.

s/ Andrew B. Johnson
OF COUNSEL